

Amendment
Docket No. 3081-A

Immunex Corporation

REMARKS

Claims 1-6 are under examination, and claims 7-21 have been withdrawn. By this amendment, claim 2 has been cancelled, and claims 1 and 4 amended. No new matter has been added by these amendments.

The claims stand rejected under 35 U.S.C. §112, first paragraph, and under 35 U.S.C. §102(e) or 35 U.S.C. §103(a). Reconsideration of the application is respectfully requested.

Rejections under 35 U.S.C. §112, First Paragraph

Claims 1-6 are rejected under 35 U.S.C. §112, first paragraph, because the specification, although enabling for *in vitro* methods, is allegedly not enabling for a method of activating the immune system in a mammal. The Examiner asserts that the specification does not adequately teach how to effectively activate the immune system in a mammal (Office Action at 3), and there are no animal model studies and data in the specification (Office Action at 4). The Examiner cites Cochlovious et al. as showing it is unclear that reliance on *in vitro* data accurately reflects the relative animal and human efficacy of the therapeutic strategy. (Office Action at 4.) Even if there were animal studies in the specification, the Examiner has cited Feldman et al., as allegedly teaching about the dilemmas of extrapolating from animal models in disease. (Office Action at 4.) Because Applicants note that IMXP-888 does not have any proliferative activity in the assays tested, the Examiner also asserts that the claimed invention is unpredictable. In addition, even though the specification describes *in vitro* data for induction of cytokine from peripheral blood lymphocytes, the Examiner asserts that this alone does not support the predictability of a method of activating the immune system in a mammal. (Office Action at 5.) Van Noort et al. is cited as indicating factors that affect the immune response such as genetic, environmental, and hormonal. The Office asserts that treatment, administration protocols depend upon the nature of the compound administered as well as the clinical condition of the subject and that in the absence of additional information the skilled artisan would not have been able to use the "undisclosed compound" for activating the immune response without undue experimentation. (Office Action at 5.) Applicants respectfully traverse this rejection.

The claims at issue relate to a method of activating the immune system in a mammal in need thereof, wherein the mammal has a condition selected from the group consisting of viral infection, bacterial infection, fungal infection, cancer, and graft v. host disorders, comprising administering to the mammal an effective amount of an IMXP-888 polypeptide,

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wherein the IMXP-888 polypeptide is encoded by a sequence that is at least 80% homologous to a polynucleotide sequence that encodes residues 18 to 375 of SEQ ID NO:3. Thus, the claims do not relate to an "undisclosed compound", but instead relate to using a defined IMXP-888 polypeptide.

As noted by the Examiner, Applicants have demonstrated through the use of *in vitro* assays particular functions for these IMXP-888 polypeptides. There is no strict requirement in patent law that, in order to enable the claimed invention, actual clinical trials must be conducted. In addition, the specification teaches in general, at pages 18, line 17 to page 19, line 17 and at page 22, line 25 to page 23, line 11, how to administer the recited IMXP-888 polypeptides. Applicants submit that having identified a function for these polypeptides, it is well within the skill of those in the art (in this case, the skilled physician) to determine appropriate administration and dosage schedules.

It is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. Section 112. The applicant need not demonstrate that the invention is completely safe.

TRAINING MATERIALS FOR EXAMINING PATENT APPLICATIONS WITH RESPECT TO 35 U.S.C. SECTION 112, FIRST PARAGRAPH-ENABLEMENT

CHEMICAL/BIOTECHNICAL APPLICATIONS, Section III.A.2.b (ii), available at <http://www.uspto.gov/web/offices/pac/dapp/mpepmain.html>. In the instant case, one of skill in the art has experience administering protein-based drugs and could determine, based upon *in vitro* activity, appropriate dosages and methods of use without undue experimentation.

As for the references cited by the Examiner, Applicants submit that these references do not support non-enablement of the claims. Feldman et al. poses the question as to how much we can rely on animal models in disease, and then appears to actually answer this question in the affirmative. Specifically, he notes that his experiments *in vitro* and *in vivo* with rheumatoid synovium led them to propose inhibiting TNF-alpha would be clinically useful (*see* second paragraph). The disclosure from Colchius et al. relates to using antibodies to fight cancer, and as such is distinct from the use of IMXP-888 polypeptides as recited in the claims herein. In particular, Colchius et al. states "Compared with their use in immunomodulation, the demands for antibodies to fight cancer are fairly different and more challenging. It is not simply a matter of binding antibodies to the tumor cell and waiting placidly for its destruction . . ." (page 37, first full paragraph). Thus, the disclosure from

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Colchius et al. does not relate to using a soluble protein to activate the immune system. The disclosure cited in Van Noort et al. merely points out that genetic, hormonal, and environmental factors affect autoimmune diseases (page 176, third paragraph), but this disclosure does not indicate that the claimed invention is not enabled or lacks utility. In fact, these are factors which those of skill in the art are trained to take into account in prescribing treatment protocols.

Finally, Applicants submit that the rejection for lack of enablement appears to be based on a doubt that the claimed invention is operative. However, there is no evidence of record that the claimed invention would not work as intended and, hence, no rejection for lack of utility under 35 U.S.C. § 101 has been made. Indeed, since the claims recite administering "an effective amount," such claims do not encompass inoperative embodiments. As in *Angstadt*, "nobody will use them [inoperative embodiments] and the claims do not cover them." *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976).

Accordingly, reconsideration and withdrawal of the rejection for lack of enablement is requested.

Also at issue is the allegation that Applicants have not taught how to make any polypeptide that is at least 80% homologous to a polypeptide sequence that encodes residues 18 to 375 of SEQ ID NO:3 to be used in the method of activating the immune system in a mammal in need. In particular, the Office asserts that it is unpredictable which changes can be tolerated in a polypeptides amino acid sequence and still retain similar functionality. Ngo et al. (1994) is cited for allegedly teaching that the relationship between the sequence of a peptide and its tertiary structure was not well understood and is not predictable. The rejection is traversed. In addition, Applicants believe that this rejection is not applicable to claim 5.

Applicants submit that one skilled in the art could, without undue experimentation, identify IMXP-888 polypeptides that are encoded by a sequence at least 80% homologous to a polynucleotide sequence that encodes residues 18 to 375 of SEQ ID NO:3, and which activate immune system cells as is taught in the specification. In addition, it is not necessary that an applicant disclose all the embodiments of his invention. *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976).

Variant DNAs that encode altered polypeptides which are encoded by a sequence at least 80% homologous to a polynucleotide sequence that encodes residues 18 to 375 of SEQ ID NO:3 can be produced by well-known procedures such as chemical synthesis, deletion, and mutagenesis techniques disclosed on pages 5-6, of the present specification. The teachings of

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the present specification, especially when taken in combination with the knowledge available in the pertinent art, enable the skilled artisan to make variant IMXP-888 polypeptides without undue experimentation. The question then becomes whether testing the encoded polypeptides for the ability to activate immune system cells, and hence establishing their utility in activating the immune system in a mammal, involves undue experimentation.

A variant polypeptide may be tested for the ability to activate the immune system using the conventional assays described in the specification. Applicants have described guidelines for determining whether a candidate polypeptide has sufficient activity at page 4, lines 19-28. Examples of suitable assay procedures for determining cytokine secretion and calcium mobilization are described in the present specification, e.g., from pages 23-27.

In *Ex parte Mark*, 12 USPQ 2d 1904, the examiner's position was that the claims encompassed innumerable muteins, while only a limited number of successful embodiments had been shown. The Examiner further asserted that undue experimentation would be required to generate the muteins encompassed by the claim using site specific mutagenesis, and to test the resulting muteins for biological activity. In reversing the examiner, the Board noted that "When it is considered that the claims . . . all require that the mutein produced retain the biological activity of the native protein, we consider the disclosure of this application to be enabling . . . The record before us establishes that for a given protein having cysteine residues, one skilled in the art would be able to routinely determine whether deletion or replacement of the cysteine residues would result in a mutein which is within the claims on appeal." *Ex parte Mark*, 12 USPQ 2d 1904, 1906-1907 (BPAI 1989).

Applicants respectfully submit that generation and testing of various IMXP-888 polypeptides that are encoded by a sequence at least 80% homologous to a polynucleotide sequence that encodes residues 18 to 375 of SEQ ID NO:3 as recited in the claims requires no more than routine experimentation. No evidence of record indicates that the assays to detect cytokine secretion or calcium mobilization are any more than conventional, well known procedures that can be conducted by the skilled artisan without undue experimentation.

As for the cited publication by Ngo et al. (only a partial copy of which was provided by the Office), this ten year-old reference merely relates to efforts at generating algorithms to predict structure from amino acid sequence. This reference does not establish that creating variants is difficult, or that testing them for functional activity is undue experimentation.

Applicants submit that by providing the amino acid sequence of IMXP-888 and appropriate assays for its function in activating immune system cells, they have provided all the information necessary to enable the skilled artisan to identify variants and fragments of

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that amino acid sequence whose use is encompassed by the instant claims without undue experimentation.

Claims 1-6 are also rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. (Office Action at 6.) The Examiner asserts that the specification fails to define all polypeptides that are at least 80% homologous to a polypeptide sequence that encodes residues 18 to 375 of SEQ ID NO:3 that can be used in a method of activating the immune system in a mammal. (Office Action at 7.)

Applicants respectfully traverse. As noted above, it is not necessary that an applicant disclose all the embodiments of his invention. *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976). And, Applicants do disclose indeed disclose the claimed invention in sufficient detail that one of skill in the art can reasonably conclude that the inventor had possession of the claimed invention. The specification describes several examples of IMXP-888 polypeptides within the recited scope (*e.g.*, human and murine soluble fragments, *inter alia*), and describes how to generate and test additional IMXP-888 polypeptides.

The Examiner cites *Lilly* for the proposition that a description of a genus of protein sequences may be achieved by means of a recitation of a representative number of polypeptide sequences, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. In *Lilly*, the patentee was found to not be in possession of the cDNA sequence encoding human insulin, because only rat insulin cDNA had been cloned. In contrast to the situation in *Lilly*, the specification does indeed show that Applicants had possession of the claimed invention. Specifically, Applicants described not only the nucleic acid molecules noted by the Examiner, but also contemplated and described a wide variety of variants of these molecules (*e.g.*, mutations, conserved changes, deletions, etc.) at pages 4-9.

The Office referred Applicants to the USPTO Guidelines for the Examination of Patent Applications under the 35 U.S.C. §112, ¶ 1 "Written Description" Requirement. Applicants have reviewed these guidelines, and submit that the claimed invention fulfills the written description requirement. In addition, Applicants refer the Examiner to the USPTO's "Synopsis of Application of Written Description Guidelines", Example 14, pages 53-55. The claim of Example 14 recites a protein having SEQ ID NO:3 and variants thereof that are at

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least 95% identical to SEQ ID NO:3 and catalyze the reaction of A->B. The disclosure of Example 14 provides a single species (SEQ ID NO:3) that has actually been reduced to practice, and describes an assay for identifying the variants having the desired catalytic activity. Applicants believe that this example is applicable to the instant case.

In view of the above, Applicants respectfully request that the rejections under 35 USC § 112, first paragraph, be reconsidered and withdrawn.

Rejections under 35 U.S.C. §102(e)

Claims 1 and 4-6 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by US Patent Publication 2002/0197674, WO 01/70977, or WO 01/00673 (Millenium).

Applicants note that the '674 publication (Genentech) is a continuation of an application filed on August 28, 2001, and that the '674 publication claims priority to approximately 40 international applications and over 40 provisional applications. Since the present application is entitled to a priority date of November 22, 2000, it is not clear on its face that the '674 publication is available as prior art under 35 U.S.C. §102(e). However, Applicants also note that one of the foreign priorities claimed by the '674 publication is PCT/US99/12252. This corresponds to publication WO99/63088, which Applicants have already made of record in the present application.

Claim 1 has been amended to recite the limitations of claim 2. As none of the cited references teach the presently claimed invention, Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejections under 35 U.S.C. §103(a)

Claims 2 and 3 are rejected under 35 U.S.C. §103(a) in view of any one of US Patent Publication 2002/0197674, WO 01/70977, or WO 01/00673, in view of US Patent No. 5,807,862. Although claim 2 has been cancelled, the limitations of claim 2 have been incorporated into current claim 1.

As the Examiner notes, US Patent Publication 2002/0197674, WO 01/70977, and WO 01/00673 do not teach a "method of activating the immune system in a mammal, wherein the mammal has a viral infection." (Office Action at 9.) However, the Examiner asserts that the '862 patent teaches a method of treating a number of diseases, including viral infection, in mammals by stimulating the immune system in response to FGF administration (citing

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columns 12 and 13, in particular). In addition, the Examiner states that humans are an obvious species of the mammal genus. (Office Action at 10.)

Applicants respectfully traverse this rejection. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Here, the cited references, even when taken together, do not teach or suggest the claimed invention. In fact, certain of the cited references teach away from the claimed invention. Furthermore, there is no motivation to combine these references.

In particular, the '674 publication does not teach or suggest each and every limitation of the claimed invention. Instead, this reference teaches away. The '674 publication speculates, based upon sequence homology to the fibroblast growth factor receptor, that "it is presently believed that PRO943 disclosed in the present application is a newly identified member of the fibroblast growth factor receptor family and may possess activity typical of that family" ('674 application, paragraph 3049). In addition, at paragraph 4361, the '674 publication also states "that certain polypeptides of the invention act to induce the expression of c-fos in pericyte cells and, therefore, are useful not only as diagnostic markers for particular types of pericyte-associated tumors but also for giving rise to antagonists which would be expected to be useful for the therapeutic treatment of pericyte-associated tumors." One of the polypeptides which the '674 publication speculates should be *antagonized* for treating pericyte-associated tumors is PRO943 (see paragraph 4362). As the currently claimed invention is drawn to a method of activating the immune system in a mammal, including a mammal with cancer, by administering IMXP-888 polypeptide (an *agonist*), the '674 publication does not anticipate the claimed invention but instead teaches away.

WO '977 states that in several tumor cell lines, FGFR-L polypeptide is shed into the culture medium, and that this suggests that the FGFR-L polypeptide extracellular domain may play roles in the growth or differentiation of tumor cells. However, nowhere does this publication teach activating the immune system in a mammal with viral infection.

Nor does WO '673 teach or suggest the claimed invention. WO '673 speculates for almost 3 pages of text that MANGO 003 and "modulators thereof" could be used to treat a large variety of many different disorders (see pages 32-34). However, WO '673 does not indicate whether one should use a MANGO 003 antagonist (a "modulator thereof") or a

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MANGO 003 agonist (also a "modulator thereof") to treat any particular one of these diseases. Furthermore, nowhere does WO '673 teach or suggest activating the immune system in a mammal with viral infection, bacterial infection, fungal infection, cancer, or graft v. host disorders by administering MANGO 003.

Nor does the '862 patent remedy the above noted deficiencies. The '862 patent relates to a class of chemical compounds which is asserted to have utility in treating disease states mediated by excess TNF or IL-1 (such as viral infection) (see col. 13, lines 3-8). The class of compounds is also asserted to have a separate utility in inhibiting FGF so as to inhibit angiogenesis or restenosis (see col. 13, lines 16-19). Simply because a class of chemical compounds is asserted to have utility in both treating viral infections and inhibiting FGF, does not teach or imply that every compound in the class which has one utility will also have the other utility. Nor does this disclosure teach or suggest using a completely unrelated compound (IMXP-888) to activate the immune system to treat viral infections.

In addition, there is no motivation to combine these references to reach the claimed invention. There is no evidence of record that IMXP-888 even has FGF-inhibitory activity, only that this protein is a member of the FGF-receptor superfamily. The '862 patent refers to inhibiting FGF, a completely different and unrelated protein. Accordingly, there is no reason to even to try to combine the cited references.

Since the cited references, alone and in combination, fail to present a *prima facie* case of obviousness, the rejections on this basis should be withdrawn.

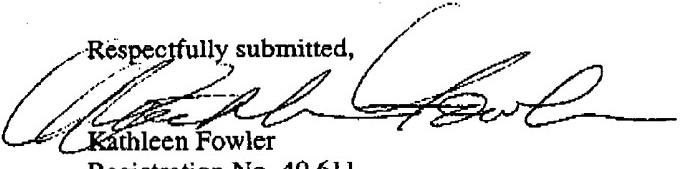
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CONCLUSION

Applicants submit that the presented claims are in condition for allowance. A favorable action is earnestly requested. Applicants' attorney invites the Examiner to call her at the number below if any issue remains outstanding.

Respectfully submitted,



Kathleen Fowler

Registration No. 40,611

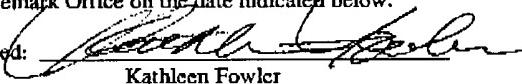
Direct Dial No. (206) 265-7847

Immunex Corporation
Law Department
1201 Amgen Court West
Seattle, WA 98119
Telephone (206) 265-7000

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Signed:



Kathleen Fowler

Date: May 18, 2004